UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,904	12/02/2003	Kei Roger Aoki	16952CON1CIP3 (BOT)	4172

7590 04/07/2008

STEPHEN DONOVAN
ALLERGAN, INC.
T2-7H
2525 Dupont Drive
Irvine, CA 92612

EXAMINER	
GUPTA, ANISH	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
04/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/726,904	AOKI ET AL.	
	Examiner	Art Unit	
	ANISH GUPTA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,29,47 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,29,47 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-29-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority Under 35 U.S.C. 119

1. The priority under 35 U.S.C. 119 to parent application 08/173,996 and 08/627,118 has been denied for the reasons set forth in the previous office action and the reasons set forth below. It should be noted, however, that the basis for denial of priority is under 35 U.S.C. 112 First paragraph Enablement for the reasons set forth in the previous office action and the reasons set forth below.

Response to Arguments

2. Applicants argue that the priority should be granted based on the evidence presented in the Brin Declaration and the newly submitted Smith Declaration. Applicants assert that the declaration by Dr. Brin, establishes that the toxin component could be obtained by well known methods in the art and one " would have been able with little or no difficulty to obtain the neurotoxic component of a botulinum toxin so as to be able to use the neurotoxic component to treat a patient with on or more of the Disorders." Applicants assert that the Brin declaration is "evidence" and should be considered. "Hence the examiner is asked to reconsider the Brin declaration which is the expert opinion by a noted clinical with many years therapeutic use of botulinum toxin, noting the actual basis for the opinion by Dr. Brin. . ."

Applicants have also submitted a declaration by Dr. Smith which states that statements made by Schantz, 1992, are clearly wrong. "The statements in Schantz 1993 are mere conjecture and unsupported opinion statements." The declaration by Dr. Smith state that the statements made in Schantz et al. are "clearly wrong." Dr. Smith asserts that there is no data or experimental evidence presented in the reference. The statements made in Schantz 1992

regarding clinical unsuitability of the neurotoxic component of boutlinum toxin has been challenged in the literature, making reference to articles from DasGupta (1994). It was known in the art, after March 1992 but before 1993, "that a storage stable formulation of the neurotoxic component could be administered to various mammal species with physiological effect." Applicants make reference to a book by Lamanna C. which states "Type A hemagglutin-free toxin causes electrocardiographic changes and a decreased heart rate (bradycardia) within minutes of injection of the toxin in rodents and dogs, the species studied." Concurrent with December 1993, it was known that neurotoxic component could be diluted, formulated and dried to prepare an active, potent formulation of the neurotoxic component. Applicants make reference to the Ph.D. thesis entitled *Characterization and stabilization of clostridium botulinum neurotoxin* by Michael C. Goodnough, published by University of Wisconsin, March 10, 1994. Applicants have submitted this reference that shows formulations of the neurotoxic component suitable for medical use of 150 kDa portion of the botulinum toxin. Based on excerpts from this thesis, Dr. Smith concludes "the person of ordinary skill in the field (i.e. a physician of ordinary ability with knowledge of or experience using a botulinum toxin, referred to hereafter as the "Physician") could obtain, formulate and clinically use a potent and effective neurotoxic component formulation prepared by using the same reagents and the same dilution, drying and reconstitution techniques known for preparing and using a clinically effective botulinum toxin complex formulation."

Dr. Smith further concludes that "the '996 application, in light of the art set forth above, clearly and explicitly discloses how the Physician can therapeutically use the neurotoxic component to effectively treat patients, that is how to use the neurotoxic component in a clinical

setting." Dr. Smith makes reference to the disclosure of the molecular weight, formulations of the toxin, the administration to the patient, etc. "Thus, it is my opinion the '996 application teaches a Physician how to formulate a clinically effective formulation of the neurotoxic component, and as well how to administer to patient a therapeutically effective neurotoxic component formulation."

In their arguments, Applicants assert that the thesis should not be underestimated. "When one remembers that Schantz 1992 states on page 89 that the neurotoxin component is unlikely to be used in a clinical setting because in Schantz's opinion the neurotoxic component is "inactivated on dilution, formulation and drying", and then notes that in direct contradiction thereto the Goodnough Ph.D thesis based on extensive experimental work states that when the neurotoxic component and the botulinum toxin complex were both seperately lyophilized and dried with albumin "recoveries on drying [the neurotoxic component] were similar to those obtained with the complexes" (see Smith dec 1115(d)G, and Goodnough thesis page 137) and that "Recovery of activity following lyophilization of purified type A and B neurotoxin does not seem to be dependant on the presence of the non-toxic binding proteins of the complex as a high percentage of toxin activity was recovered using the same formulation as that used for the type A and B toxin complexes." (Smith dec 1115(d)H and Goodnough thesis page 142, emphasis added), then it could not be clearer that Schantz 1992 was wrong, that is that a stable formulation of the neurotoxic component can be prepared using the same formulation made by the same process used to make a stable botulinum toxin complex formulation. Each of these four bases show that while the statements in Schantz 1992 do in fact teach away from clinical use of the neurotoxic component, these statements in Schantz 1992 are wrong."

Applicants assert again "Schantz 1992 says what it says and therefore when Schantz 1992 states that the neurotoxic component is unlikely to be used clinically Schantz 1992 teaches away from and renders unobvious the claimed invention. Applicants have presented evidence that Schantz 1992 was wrong and that therefore a person of ordinary skill could in fact make and clinically use the neurotoxic component, as claimed, using the disclosure and guidance provided by the '996 application. Hence, Schantz does still render the claims not obvious (i.e. Schantz says what it says) but does not render the specification non- enabling (i.e. Schantz was wrong and the specification in enabling). As stated in Singh v. Brake, 65 USPQ 2d, 1641 at 1650 (Fed. Cir. 2003)"Although the questions (1) whether or not a reference 'teaches away' from a claimed invention and (2) whether or not a claimed invention provides 'unexpected results' are relevant in determining whether not a claimed invention would have been obvious, they are not the primary questions bearing on enablement".

Applicants arguments have been fully considered but have not been found persuasive.

First, both declaration by Dr. Brin and Dr. Smith have been given their full consideration. However, the declaration by Dr. Brin and Dr. Smith do not provide ample evidence to support the position that Applicant disclosure in enabling.

The standard for declaration and affidavit in the context of enablement is as follows. "A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the **amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement.**" See MPEP 2164.05. "It should be noted also that it is not opinion evidence directed to the ultimate legal question of enablement, but rather factual evidence directed to the amount of time and effort and level of knowledge

required for the practice of the invention from the disclosure alone which can be expected to rebut a prima facie case of nonenablement." See MPEP 2105. Furthermore,"[w]hether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art. The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed." See MPEP § 2164.05(a). Finally, "To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." See MPEP 2164.05.

The issue here is whether the art, as of the filing date of '996, provided ample guidance on how to make purified botulinum toxin useful in a clinical setting (treatments). As stated in the previous office action, the Brin Declaration did not provide any evidence to counter the contentions raised by Schantz et al. While one of ordinary skill in the art may be able to make the neurotoxic component the Declaration does not set forth how one of ordinary skill in the art can use the toxic component as claimed to treat the disorders as claimed "with little or no difficulty." The question was not whether one could make or isolate the purified toxin but whether one could use it in a clinical setting. The Brin declaration did not provide any evidence for this conclusion.

The declaration by Dr. Smith, while providing ample opinion evidence, does not provide sufficient evidence to counter the conclusions of Schantz. The declaration states that the Schantz does not provide any evidence to support the conclusion. However, reviewing Schantz, the reference disclose, on page 82, pH, dilution at low concentrations, pH of greater than 7.3 the neurotoxin is liberated as the basis for its conclusion. Dr. Smith's declaration relies upon the reference of DasGupta as evidence that the statements made in Schantz are incorrect. However, this reference is post dated to Applicants invention. Remember that "The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date." See MPEP 2164.05(a) Prior to Applicants filing date, it was believed (and Applicants have asserted his on numerous occasions) purified botulinum toxin is so labile that it would not be used in clinical settings. The declaration simply does not provide evidence to the contrary prior to December of 1993.

The Dr. Smith declaration also asserts that the data presented in Lamanna C. which states "Type A hemagglutin-free toxin causes electrocardiographic changes and a decreased

heart rate (bradycardia) within minutes of injection of the toxin in rodents and dogs, the species studied." However, this does not resolve the issue at hand. Namely how does one of ordinary skill in the art go about making the pure neurotoxin clinically viable. The Schantz reference does not teach nor imply that pure toxin does not exert an effect. Rather that the instability of the toxin results in ineffectiveness in the clinical setting. The teachings of a non clincal setting, i.e. rodents and dogs, just do not correlate to one another. In fact, on 3-29-06 Applicants concluded as much when they stated because of the teachings of Shantz "one of ordinary skill in would not be impelled to combine teachings of the. . . (use of purified botulinum toxin in a non-clinical setting, i.e. rat experiment) with the teachings of the. . .(use of complexed botulinum toxin in a clinical setting . . ." Applicants have implied on the record that "non clincal" setting are not correlative of "clinical setting."

Applicants make reference to the thesis by Dr. Goodnough. Again "The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date." See MPEP 2164.05(a) Prior to Applicants filing date, it was believed (and Applicants have asserted his on numerous occasions) purified botulinum toxin is so labile that it would not be used in clinical settings. The declaration simply does not provide evidence to the contrary prior to December of 1993 since the reference relied upon was publicly available after the filing date of the instant application. Assuming arguendo that the date was not in issue, the reference does not provide any evidence to establish that the pure neurotoxin is can be used in a clinical setting. Nothing in the reference establishes that the toxin was used in a clinical setting. The reference merely concludes that the use of it as a pharmaceutical is "possible." All of the testing parameters were done on a "non clinical" setting which involved

lethal doses to mice (see page 133). The lyophilization experiments did not conclude the clinical viability of the lyophililzed product. The Schantz reference stated that "No clinical trials on primates have been performed with purified neurotoxin" (see page 89 of Schantz) and "[b]ecasue of its labiality the neurotoxin [pure] is not practical for medical applications." (see Page 82 of Schantz). The reference simply does not establish that labiality is not an issue in the clinical setting. Applicants concluded as much when they stated because of the teachings of Shantz "one of ordinary skill in would not be impelled to combine teachings of the. . . (use of purified botulinum toxin in a non-clinical setting, i.e. rat experiment) with the teachings of the. . .(use of complexed botulinum toxin in a clinical setting . . ." Applicants have implied on the record that "non clinical" setting are not correlative of "clinical setting." Thus, to date, Applicants have not provided any evidence on the record that before Dec. 28, 1993, the filing date of '996 application, that pure botulinum toxin could be formulated to make it viable in a clinical setting.

Finally, once again, especially since Applicants have again asserted so and for clarity of the record, it was Applicants who stated in their response, **"[A]t the time of the filing of the present application, one of ordinary skill would not consider using only the purified botulinum toxin component of the botulinum toxin in clinical settings**. For example, in 1992, Schantz et al. (hereinafter the "Schantz reference") clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings. . ." It was Applicants, the inventors of numerous Patent on Botulinum toxin, forwarded this position in Schantz, not as "mere conjecture and unsupported opinion statements," but as facts (and still seem to do so today based on the statements made on page 10-11 of the response). Applicants

are now arguing to the contrary. However, Applicants recent response does not provide ample evidence to overcome Applicants own belief that "**[A]t the time of the filing of the present application, one of ordinary skill would not consider using only the purified botulinum toxin component of the botulinum toxin in clinical settings**. For example, in 1992, Schantz et al. (hereinafter the "Schantz reference") clearly stated that purified botulinum toxin is so labile that it would not be used in clinical settings. . ." What is more puzzling is that Applicant have again stated that Schantz "says what it says." It is unclear how, after asserting that Schantz is wrong, rely on statements therein and assert that it renders unobvious the claimed invention because "it says what it says." The standards for enabling disclosure is the same for both the prior art and the patent application. Again, Applicants have not set forth a basis to demonstrate such a distinction. The standards to render a reference non-enabling are the same as the standards to render a specification non-enabling under 112 first paragraph. That is, both, require the same analysis the state of the prior art, the amount of guidance provided within reference, the presence of working examples etc. . ., to allow one to determine how to make and use the invention. Applicants position is absolutely contradictory in nature, arguing on one hand Schantz is wrong (when used against them in non enabling disclosure), however is correct because it "says what it says" (when not relied upon in the rejection but used by Applicants as evidence to support non-obviousness). In essence, if Applicants truly believe that the statements in Schantz are wrong, how can Applicants keep asserting this incorrect statement as evidence for nonobviousness?

Since the specification did not disclose methods that one of ordinary skill in the art could utilize to render the pure toxin clinically effective and given the state of the art as recited by

Schantz, one would be burdened with undue experimentation to practice the claimed invention. Thus, since the parent application does not provide enablement for the claimed subject matter of the later-filed application in compliance with the requirements of 35 U.S.C. 112, first paragraph, the priority is denied for 08/173,996.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-2, 4-5, 29, 47, 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balkan et al. or Han et al. in view of Kohl et al. and Tsc et al. and Aoki et al. (US 6,113,915) for the reasons set forth in the previous office action and the reasons set forth below.

Applicants argue that the rejection cannot be maintained since they are entitled to priority to December 28, 1993. If priority is granted Han and Aoki cannot be prior art. Second

Applicants again assert that combination of the remaining references in the rejection, Anderson (1992) and Tse (1982), cannot render the amended claims obvious because Schantz, discloses on page 89 that "it is unlikely that [the neurotoxic component] will be used in a clinical setting", thereby showing that the prior art teaches away from a combination of Tse with Anderson to thereby allegedly teach the claimed invention."

Applicants arguments have been fully considered but have not been found persuasive.

First, the priority issue has been addressed above. Since priority is still denied and the effective filing date is 5-21-03 (filing date of 10/443593), Han and Aoki et al. are prior art to the claimed invention. Secondly, with respect to Schantz et al. Kohl et al. teaches the administration of botulinum toxin NT-201, a highly purified botulinum toxin that consists of pure neurotoxin. The results showed that that the paralytic effect of appears to be faster with NT-201 based on 20% CMAP decline. The maximum effect of this toxin was comparable to the complexed neurotoxin (see page 165). Note that the subjects used were human male volunteers. Note that this reference was cited in Hunt (US2003/0118598), which has the same Assignment as the instant application, as the basis to conclude that pure botulinum toxin can be formulated into pharmaceutical formulations for human use. "[P]ure botulinum toxin has been used in humans. see e.g. Kohl A., et al., Comparison of the effect of botulinum toxin A Botox (R)) with the highly-purified neurotoxin (NT201) in the extensor digitorum brevis muscle test, *Mov Disord* 2000;15(Suppl 3):165. Hence, a pharmaceutical composition can be prepared using a pure botulinum toxin." (see page 4, paragraph 043).

It should be noted that Aoki et al. teach that 150kda portion of the toxin can be obtained form botulinum toxin A-G (see col. 5, lines 1-25). Thus, it would have been obvious to use the

150kda portion of any of seven types of toxin for the treatment of cervical dystonia.

Rejection is maintained.

4. Claims 1-2, 4-5, 29, 47, 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balkan et al. or Han et al. in view of Khol et al. and Aoki et al. (US 6,113,915) and Aoki et al. (20010018415) for the reasons set forth in the previous office action and the reasons set forth below.

The claims are drawn to a method of treating strabismus using therapeutically effective amount of neurotoxin component of the botulinum toxin free of botulinum toxin protein.

For this rejection Applicants argue that Aoki patent is not prior art with regards to the amended claims. Aoki 2001-018415 is a divisional application having the same specification and the same effective filing date as the '996 application, also cannot be prior art with regard to the amended claims. "Hence, if priority to the December 28, 1993 filing date of the '996 application is granted the rejection is obviated and renders moot [this] rejection."

Applicants arguments have been fully considered but have not been found persuasive.

The priority issue has been addressed above. Since priority is still denied and the effective filing date is 5-21-03 (filing date of 10/443593), both Aoki et al. references are prior art to the claimed invention.

Rejection is maintained.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can normally be reached on (571) 272-0562. The fax phone number of this group is (571)-273-8300.

/Anish Gupta/
Primary Examiner, Art Unit 1654